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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/578,453	MALLET ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 16-26 are pending.

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be to directed to Brian Whiteman, Art Unit 1635.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications and the status of the application except when the reference is to a prior application of a CPA assigned the same application number.

Specification

Upon further review of the application, this application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

Claims 17, 18, 19, 20, and 21 are objected to because of the following informalities: The phrase "A recombinant virus according to claim 16" is an improper phrase for a dependent claim. Suggest amending the phrase to read -- The recombinant virus according to claim 16 --. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims, as best understood, are readable on a genus of a recombinant virus selected from the group consisting of adenovirus, adeno-associated virus and herpes virus, said recombinant virus comprising a nucleic acid consisting of a genus of nucleic acid encoding a mutated from of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration in vitro. The specification contemplates dominant-negative mutants of p53 consisting essentially of inactive mutated form, which are capable of entering into competition with the wild-type protein for the interaction of DNA (page 4, lines 17-28). The specification provides sufficient

description for a nucleic acid encoding a p53Val135-mutated form of p53. However, the specification does not describe if p53Val135 caused neuronal degeneration in vitro and that this mutant of p53 or any other mutant of p53 could antagonize such effects of p53 on neuronal cells in vitro. In addition, the specification does not provide sufficient description of a genus of nucleic acids encoding a mutated form of p53 that possess the claimed biological activity in vitro. The activity in claims 16 and 22 is different than the activities observed in the examples in the specification as filed. Example 1 displays a correlation between lack of p53 expression and reduction in the volume of infarct upon occlusion of the cerebral artery in p53 knockout mice as compared to control mice. Example 2 discloses that anti-p53 antisense (not a double negative p53) partially inhibits cell death induced by glutamate in primary culture of cortical neurons. The specification does not teach what nucleotides of a nucleic acid codes for a p53 protein that antagonizes wild-type p53-mediated neuronal cell degeneration in vitro; for example, there is no structure-function relationship regarding putative nucleic acid encoding a mutated p53 and having the ability to antagonize wild-type p53-mediated neuronal cell degeneration in vitro. There is no description in the instant specification concerning what sequences/structures/domains within the p53 protein are necessary for the claimed activity of a mutated p53 when transfected in neuronal cells in vitro. In the absence of a description of what sequences/structures/domains are absolutely required for the protein to have the claimed activity when introduced into neuronal cells in vitro, the skilled artisan cannot envision what mutated p53 is embraced by the claimed genus. The prior art is absent for p53 mutated proteins that antagonize wild-type p53 neuronal cell degeneration in vitro. Therefore, functional descriptions alone, as recited in claims 16 and 22, do not provide any structural information relating to what the recited nucleotide sequences

are from claims only reciting such. It is not apparent that on the basis of the applicants' disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the claimed invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of nucleic acids that must exhibit the disclosed biological functions as contemplated by the specification.

It is not sufficient to support the present claimed invention directed to a genus of nucleic acids encoding a mutated form of p53, which antagonizes wild-type p53-mediated neuronal cell degeneration by contemplating the claimed genus. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of nucleic acids that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of nucleic acids that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-

filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicants' arguments filed 11/8/04 have been fully considered but they are not persuasive. Applicants argue that the rejection is improper because it is based on mischaracterizations of both the scope of the claims and the scope of the support taught by the application. Applicants argue that all pending claims require that the nucleic acid construct be contained in a recombinant virus. Applicants argue that at the bottom of page 4 of the instant specification forms of mutated p53 (double negative mutants) known in the prior art capable of use in the present invention.

With respect to applicant's argument that the rejection is improper because it is based on mischaracterization of both the scope of the claims and the scope of the application, the argument is not found persuasive because when the claims analyzed in light of the specification, the claims encompass a genus of nucleic acids encoding a mutated form of p53 which antagonizes wild type p53 neuronal cell degeneration in vitro.

With respect to applicant's argument that the claims require that the nucleic acid construct be contained in a recombinant virus, the argument is not found persuasive because the rejection is not based on a generic recombinant virus selected from the group consisting of herpes virus, adenovirus, adeno-associated virus comprising a genus of nucleic acids. The rejection is based on specific recombinant viruses comprising a nucleic acid consisting of nucleic

acids encoding a mutated form of p53, which antagonizes wild-type p53-mediated neuronal cell degeneration in vitro.

With respect to applicants' argument that on page 4 of the instant specification provides support for a genus of mutated p53, the argument is not found persuasive because as stated in the rejection, the specification does not describe if p53Val135 caused neuronal degeneration in vitro and that this mutant of p53 or any other mutant of p53 could antagonize such effects of p53 on neuronal cells in vitro.

Claims 16-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (A) a recombinant virus selected from the group consisting of adenovirus, adeno-associated virus and herpes virus, wherein said recombinant virus comprises a nucleic acid selected from the group consisting of (i) a DNA comprising a binding site for p53, wherein the DNA consists of SEQ ID NO: 2; and (ii) a nucleic acid encoding an antisense RNA consisting of SEQ ID NO: 1, which inhibits expression of p53 and (B) a method of inhibiting glutamate mediated ischemic neuronal cell death in culture by administering the cells with a nucleic acid, which encodes an antisense RNA which inhibits expression of p53 wherein said antisense RNA consists of the sequence disclosed in SEQ ID NO: 1, does not reasonably provide enablement for the claimed vectors comprising a nucleic acid encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration in vitro or for a method for inhibiting toxicity using all nucleic acids encompassed by the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claimed invention encompasses (i) any nucleic acid that encodes any mutated form of p53 which antagonizes wild type p53-mediated neuronal cell degeneration in vitro; (ii) any site for binding of p53 to DNA; (iii) any nucleic acid that encodes an antisense RNA which inhibits expression of p53 and (iv) an active variant of SEQ ID NO 2. Additionally, the invention encompasses inhibiting toxicity in cultured neuronal cells by delivering the claimed nucleic acids to the cells.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

First, the specification is not enabling for the claimed polynucleotides of claims because the specification does not teach how to make a polynucleotide that encodes a mutant of p53 that would antagonize the wild type p53 mediated neuronal cell degeneration. The specification on page 7, lines 13-21 makes a general statement, which reiterates what, is recited in instantly presented claims. On page 4, lines 17-28, the specification lists a p53Val135 mutant of p53 and that the mutant may be a negative dominant mutant of p53 consisting essentially of inactive

mutated form which competes with the wild type protein for binding to DNA. The specification, however, does not provide any guidance to make such a dominant negative mutant or any mutant of p53, what parts of the protein were to be mutated or altered in order to get a mutant that would meet the functional requirements claimed. Regarding the p53Val135, the specification does not provide any evidence whether this mutant would have antagonized the wild type mediated p53 mediated neuronal cell degeneration. While the art of record (Moberg et al Journal of Cellular Biochemistry 49:208-215, 1992 or Michalovitz et al Cell 62: 671-680, 1990) disclose that the p53Val135 is a temperature sensitive mutant of p53, which is transforming at one temperature, these arts do not teach or provide any guidance or evidence that the protein antagonizes the function of wild type p53. The prior art does not teach what mutant will be able to antagonize the neuronal cell degenerative effects of p53. As for the specification, it does not provide any evidence either that p53 caused neuronal cell degeneration and that this mutant of p53 or any other mutant of p53 could antagonize such effects of p53 on neuronal cell. It is noted that the specification in example 1 teaches that a p53 knockout mouse showed a higher mean volume of infarct compared to a control mouse (see the table on page 15). However, these results in no way indicate that p53 is responsible for neuronal cell death in the knockout mouse. While the art of record (Chopp et al. Biochemical and Biophysical Research Communications, 1992) teaches association of increased expression of p53 with ischemic parts of brain, neither the specification nor the art of record teaches that any mutant of p53 could inhibit any toxicity in neuronal cell culture. In summary, neither the art of record or the specification as filed teaches how to make and use a mutant p53 that would have a function as recited.

The specification does not teach what parts or amino acids of p53 protein could be mutated to obtain a protein that would antagonize the wild type activity for inhibiting neuronal cell death. It is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein (see second paragraph in Rudinger J in Peptide Hormones. Editor Parsons JA. Pages 1-7, 1976, University Park Press, Baltimore). Rudinger further add, "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see conclusion on page 6). While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions where the biological activity resides or regions directly involved in binding, stability, or catalysis; and in providing the correct three-dimensional spatial orientation for biologically active or binding sites, or for sites which represent other characteristics/properties of the protein. These or other regions may also be critical determinants of antigenicity of the protein of interest. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990. Science, Vol. 247, pp. 1306-1310, especially p. 1306, column 2, paragraph 2; and see Ngo et al, The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merzer (ed.), pages 433&492-495). Applicant has provided little or no guidance beyond the mere general statements to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein,

which could be mutated or altered so as to make a mutant protein that would have antagonized the neuronal cell degeneration effects of wild type p53.

Regarding the sequence of the site for DNA binding (and variants thereof) and antisense RNA encoding nucleic acids, the specification discloses a consensus p53 binding domain (SEQ ID NO 2) taught in the art (Funk et al. Molecular and Cellular Biology 1992) and an antisense oligonucleotide sequence (SEQ ID NO 1). Except for these two sequences, the specification does not provide any specific guidance how to make any other p53 DNA binding domain or a variant of such a sequence or any other antisense nucleic acid. Again, except for mere general statements in the specification (such as on page 4 of the specification), the specification does not provide any specific teaching as to how to make such DNA binding sites (variants of these) or antisense RNA encoding nucleic acids. On page 4, applicants list certain WO documents, however, none of these documents teach how to make the claimed nucleic acid that would have the function as claimed. While it would have been routine to make mutants, it was not routine in the art to make random mutations in a given nucleic acids to produce mutants or variants. It would have required undue experimentation to produce mutants or variants as encompassed by the claimed invention because neither the specification nor the art of record provides any specific guidance as to what parts of the nucleic acid to alter such as to produce nucleic acid that would have desired function and this was not routine in the art.

Regarding the nucleic acid encoding an antisense RNA, at the time of the invention, the art of designing antisense oligonucleotides for inhibiting gene expression was unpredictable. For example, Sherman (Annals of NY Acad. Sci. 616:201-204, 1990), discussed some of the limitations and potential problems associated with antisense targeted gene expression inhibition.

For example, antisense sequences directed against different regions of a target nucleic acid would be differentially active, such as the antisense sequences that hybridize with the 5' end of a mRNA would have different levels of effects on the expression of the targeted gene, compared to sequences targeting the internal regions of the mRNA because they would target different steps of gene expression. These factors are further compounded by the fact that base compositions as well as tertiary structure of the target sequence will determine the accessibility of the target sequence to the antisense sequence. Additionally, in order to be maximally effective, the antisense molecules must reach their respective intracellular target in an intact state. In another review, Rojanasakul (Advanced Drug Delivery Reviews 18:115-131, 1996) analyzed the issue: can antisense work in living system and discusses issues such as, how can antisense oligonucleotides be targeted to diseases cells, sparing normal cells and many instances one would see more effect on gene expression with a control oligo than the target oligo. Another issue is their degradation and effects of the degradation products on gene expression and cellular metabolism. It is noted that the specification neither provides any specific guidance to make antisense oligonucleotides nor does it teach as to how an artisan of skill would have addressed art recognized limitations associated with antisense oligonucleotide design and usage for inhibition of gene expression. An artisan of skill would have required undue experimentation of make the antisense nucleic acid as broadly claimed because the art was not routine and was unpredictable at the time of the specification.

With respect to claims 22-26 directed to a method of inhibiting toxicity in cultured neuronal cells using the claimed nucleic acids, the specification does not teach one skilled in the art how to practice the claimed method. The method reads on inhibiting toxicity in cultured

neuronal cells, but does not recite what toxicity is being inhibited in the cells using the claimed nucleic acids. In view of a lack of a definition in the specification for what toxicity is being inhibited, the claims must be considered broad. The prior art is absent for using any of the claimed nucleic acids in a method of inhibiting toxicity in cultured neuronal cells. The applicants teach using SEQ ID NO: 1 to inhibit glutamate mediated ischemic neuronal cell death in cultured neuronal cells. In addition, the specification as filed and the prior art do not teach using nucleic acids encoding a mutated form of p53 or nucleic acid consisting of the site for binding of p53 to DNA that would have the function as claimed in the method. The applicants did not teach how to reasonably extrapolate from contemplating a genus of nucleic acids encoding a mutated form of p53, which antagonizes wild-type p53-mediated neuronal cell degeneration in vitro to inhibiting an unspecified toxicity in cultured neuronal cells using a genus of nucleic acids encoding a mutated form of p53. Furthermore, for the reasons listed above, the specification as filed does not teach the skilled artisan how to use a genus of nucleic acids encoding a mutated form of p53. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

In conclusion, the specification as filed does not provide sufficient guidance for an artisan of skill to have practiced the claimed invention commensurate with the full scope of the claims and therefore, limiting the scope of the claimed invention to (A) a recombinant virus selected from the group consisting of adenovirus, adeno-associated virus and herpes virus, wherein said recombinant virus comprises a nucleic acid selected from the group consisting of (i) a DNA comprising a binding site for p53, wherein the DNA consists of SEQ ID NO: 2; and (ii) a nucleic

acid encoding an antisense RNA consisting of SEQ ID NO: 1, which inhibits expression of p53 and (B) a method of inhibiting glutamate mediated ischemic neuronal cell death in culture by administering the cells with a nucleic acid, which encodes an antisense RNA which inhibits expression of p53 wherein said antisense RNA consists of the sequence disclosed in SEQ ID NO: 1 is proper.

Applicants' arguments filed 11/8/04 have been fully considered but they are not persuasive. Applicants' argue that the rejection should fail because it seems to be improper argument about the utility of the claimed invention, and not actually to the enablement issue. The undersigned attorney respectfully notes that the specification and the originally filed claims contain clear statements of the applicants that the instantly claimed p53 mutants antagonize p53-caused neuronal cell degeneration and the examiner has not provided any scientific evidence to doubt applicants' statements. It is improper, in any event, for these utility concerns to be miscast as an enablement rejection.

With respect to applicants' argument that the rejection is about utility and not actually about enablement, the argument is not found persuasive because the enablement rejection is based on the In Re Wands Factors and that the instant specification failing to teach one skilled in the art how to make and/or use the claimed recombinant viruses or claimed method. See MPEP 2164. The rejection is not addressing utility of the claimed invention. If that were the case, then a 101 utility would have been made against the claims.

With respect to applicants' argument that applicants' statements that the instantly claimed p53 mutants antagonize p53 neuronal cell degeneration, the argument is not found for the

reasons of record. The applicants have not specifically pointed out where in the instant specification (e.g., page, line) the applicants teach that the instantly claimed p53 mutants antagonize p53 neuronal cell degeneration in vitro. In addition, in the amendment for claims 16-26 filed on 5/26/00, the applicants state that support may be found in the specification and in cancelled claims 11-22. However, claims 11-22 do not recite the statement and the applicants do not specifically point out where the support for these claims may be found in the specification. Therefore, as stated in the enablement rejection, the art of record or the specification as filed do not teach how to make and use a mutant p53 that would have a function as recited.

With respect to applicants' arguments that the examiner failed to provide any scientific evidence to doubt the applicants' statement, the argument is not found persuasive because the enablement rejection is based on the In Re Wands Factors and prior art is one of the factors under the Wands Factors. The enablement rejection cites several journal articles supporting the enablement rejection and the applicants have not addressed or have disregarded the articles cited in the enablement rejection of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 16-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "the site for binding of p53 to DNA" in claims 16 and 22 and is a relative term which renders the claims indefinite. The term "the site for binding of p53 to DNA" is not

defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims are directed a recombinant virus comprising a nucleic acid, however, step b) does not recite a nucleic acid. Step b) recites "the site for binding of p53 to a DNA" and the claims does not define what DNA or what the site consist of. There are several DNA binding sites for p53 and the claims indicate that there is only one binding site for p53. In addition, it is unclear if "the site" is part of p53 that binds DNA; a DNA sequence that p53 binds to or something else. Replacing the phrase with -- a DNA comprising a binding site for p53 -- would be remedial.

Claims 17-21 and 23-26 are rejected because the claims depend on claim 16 or claim 22.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 16, 17, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Roth et al. (US 6,017,524) as evident by Chatterjee et al. (US 5,474,935). The claims read on a recombinant adenovirus or a recombinant adeno associated virus comprising a nucleic acid consisting of an antisense RNA, which inhibits expression of p53.

Roth teaches using an expression vector comprising antisense p53 (column 32). Roth teaches that a recombinant retrovirus, recombinant adenovirus or recombinant adeno associated virus (AAV) can be used to introduce antisense into cells (columns 5-7).

Roth does not specifically teach that recombinant adeno associated virus is replication defective. However, AAV is a non-pathogenic, replication-defective parvovirus. See '935, column 14. Thus, Roth anticipates a replication defective AAV.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16, 17, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (US 5,087,617) taken with Roth et al. (US 6,017,524), Srivastava (US 6,261,834), Levrero et al. (Gene, 1991, cited on a PTO-892) or Kufe et al. (US 5,565,334).

The claimed invention is directed to recombinant viruses comprising nucleic acid encoding antisense p53, wherein recombinant viruses are selected from herpes virus, adenovirus, and adeno-associated virus.

Smith discloses a method of inhibiting p53 in vitro tumor cells by administering a plasmid encoding antisense p53 RNA (column 5). However, Smith does not specifically teach a recombinant virus selected from group consisting of adenovirus, adeno-associated virus, and herpes virus comprising antisense p53.

However, at the time the invention was made, recombinant viruses were well known in the art as vectors for nucleic acid transfer and expression of a nucleic acid of interest in a wide range of animal cells. Roth teaches using an expression vector comprising antisense p53 (column 32). Roth teaches that the vector can be a recombinant retrovirus, recombinant adenovirus or recombinant adeno associated virus can be used to introduce antisense into cells (columns 5-7). Srivastava teaches using a recombinant adeno associated virus comprising a heterologous gene encoding antisense RNA (column 7). Levrero discloses a recombinant defective adenovirus for the purpose of harboring foreign nucleic acid *in vitro* (page 195). Kufe

teaches using suitable gene delivery systems for delivering DNA (e.g., antisense) to targeted cells, including liposomes, receptor-mediated delivery systems, naked DNA, and viral vectors such as herpes virus, retroviruses, and adenoviruses, among others (columns 2-3).

Accordingly, in view of the prior art represented by Roth, Srivastava, Levrero, and Kufe, one of ordinary skill in the art would have had sufficient motivation to produce recombinant viruses, in particular recombinant adenoviruses, recombinant herpes virus, and recombinant adeno associated viruses comprising antisense p53 with a reasonable expectation of success.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Smith taken with Roth, Srivastava, Levrero or Kufe, namely to produce recombinant viruses comprising nucleic acid encoding antisense p53, wherein recombinant viruses are selected from herpes virus, adenovirus, and adeno-associated virus. One of ordinary skill in the art would have been motivated to produce any of the recombinant viruses, as a matter of designer choice, because herpes virus, adenovirus and adeno-associated virus were well known in the art for delivering DNA to a cell. Furthermore, the applicants do not teach any unexpected property of the recombinant virus over the prior art.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 16, 17, and 20, have been considered but are moot in view of the new ground(s) of rejection.

Claims 16, 18, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Funk et al. (Molecular and Cellular Biology, 1992) taken with Srivastava (US 6,261,834), Levrero et al. (Gene, 1991) or Kufe et al. (US 5,565,334).

The claimed invention is directed to recombinant viruses comprising nucleic acid comprising SEQ ID NO: 2, wherein recombinant viruses are selected from herpes virus, adenovirus, and adeno-associated virus.

At the time of the claimed invention, the essential element for insertion into recombinant viruses, nucleic acid comprising SEQ ID NO: 2, was disclosed in the prior art. Funk et al. teach a specific DNA binding site for p53 identical to that of SEQ ID NO: 2 (page 2866 and abstract) and its cloning into an expression plasmid (page 2867). However, Funk does not specifically teach a recombinant virus selected from group consisting of adenovirus, adeno-associated virus, and herpes virus comprising SEQ ID NO: 2.

However, at the time the invention was made, recombinant viruses were well known in the art as vectors for nucleic acid transfer and expression of a nucleic acid of interest in a wide range of animal cells. Srivastava teaches using a recombinant adeno associated virus comprising a heterologous gene (column 7). Levrero discloses a recombinant defective adenovirus for the purpose of harboring foreign nucleic acid *in vitro* (page 195). Kufe teaches using suitable gene delivery systems for delivering DNA to targeted cells, including liposomes, receptor-mediated delivery systems, naked DNA, and viral vectors such as herpes virus, retroviruses, and adenoviruses, among others (columns 2-3).

Accordingly, in view of the prior art represented by Srivastava, Levrero and Kufe, one of ordinary skill in the art would have had sufficient motivation to produce recombinant viruses, in

particular recombinant adenoviruses, recombinant herpes virus, and recombinant adeno associated viruses comprising SEQ ID NO: 2 with a reasonable expectation of success.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Smith taken with Srivastava, Levrero or Kufe, namely to produce recombinant viruses comprising nucleic acid comprising SEQ ID NO: 2, wherein recombinant viruses are selected from herpes virus, adenovirus, and adeno-associated virus. One of ordinary skill in the art would have been motivated to produce any of the recombinant viruses, as a matter of designer choice, because herpes virus, adenovirus and adeno-associated virus were well known in the art for delivering DNA to a cell. Furthermore, the applicants do not teach any unexpected property of the recombinant virus over the prior art.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 16, 18, and 20 have been considered but are moot in view of the new ground(s) of rejection.

Claims 16, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michalovitz et al. (Cell 62: 671-680, 1990) taken with Srivastava (US 6,261,834), Levrero et al. (Gene, 1991) or Kufe et al. (US 5,565,334).

The claimed invention is directed to recombinant viruses comprising nucleic acid encoding p53Val135 mutated of p53, wherein recombinant viruses are selected from herpes virus, adenovirus, and adeno-associated virus.

At the time of the invention, Michalovitz et al. taught the transfection of rat embryo fibroblasts with an expression vector encoding p53Val135 mutant and that the mutant is a temperature sensitive mutant whose expression can be modulated by changing the temperature of the culture medium cells are grown (abstract, Figure 1, Table 1). However, Michalovitz does not specifically teach a recombinant virus selected from herpes virus, adenovirus, and adeno-associated virus comprising a nucleic acid encoding p53Val135 mutant. It is noted that while the art of Michalovitz et al does not specifically teach inhibition of neuronal cell degeneration by a mutant p53. Please note that these claims are product claims and very little weight is given to an intended use as an antagonizer of wild type p53-mediated neuronal cell degeneration *in vitro*. See MPEP 2122.

However, at the time the invention was made, recombinant viruses were well known in the art as vectors for nucleic acid transfer and expression of a nucleic acid of interest in a wide range of animal cells. Srivastava teaches using a recombinant adeno associated virus comprising a heterologous gene (column 7). Levrero discloses a recombinant defective adenovirus for the purpose of harboring foreign nucleic acid *in vitro* (page 195). Kufe teaches using suitable gene delivery systems for delivering DNA (e.g., antisense) to targeted cells, including liposomes, receptor-mediated delivery systems, naked DNA, and viral vectors such as herpes virus, retroviruses, and adenoviruses, among others (columns 2-3).

Accordingly, in view of the prior art represented by Srivastava, Levrero, and Kufe, one of ordinary skill in the art would have had sufficient motivation to produce recombinant viruses, in particular recombinant adenoviruses, recombinant herpes virus, and recombinant adeno

associated viruses comprising a nucleic acid encoding p53Val135 mutated form of p53 with a reasonable expectation of success.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Smith taken with Srivastava, Levrero or Kufe, namely to produce recombinant viruses comprising nucleic acid encoding p53Val135 mutated of p53, wherein recombinant viruses are selected from herpes virus, adenovirus, and adeno-associated virus. One of ordinary skill in the art would have been motivated to produce any of the recombinant viruses, as a matter of designer choice, because herpes virus, adenovirus and adeno-associated virus were well known in the art for delivering DNA to a cell. Furthermore, the applicants do not teach any unexpected property of the recombinant virus over the prior art.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 16, 20, and 21 have been considered but are moot in view of the new ground(s) of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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